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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/437,450	11/10/1999	JONATHAN H. FREEDMAN	1579-315	7992

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EXAMINER	
PARAS JR, PETER	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/437,450	FREEDMAN ET AL.	
	Examiner	Art Unit	
	Peter Paras, Jr.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *1-6,8-10,12-14 and 16-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7,11 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 January 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's amendment received on 3/4/03 has been entered. Claims 1-19 are pending. Claims 7, 11, and 15 are under current consideration.

Election/Restrictions

Claims 1-6, 8-10, 12-14, and 16-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 16.

Applicants continue to argue that Inventions I-IV should be rejoined because each of the nucleotide sequences set forth in Groups I-IV, respectively, are derived from the same predicted gene. Applicants have also asserted that the present restriction requirement fails to comply with the Patent Office's determination that up to 10 independent and distinct nucleotide sequences would be examined in a single application without restriction. See pages 2-3 of the amendment received on 3/4/03.

In response, the Examiner asserts that it appears that the nucleotide sequences [SEQ ID NO: 34, SEQ ID NO: 50, SEQ ID NO: 40, and SEQ ID NO: 14] embraced by Inventions I-IV respectively are structurally and chemically different as evidenced by their different sequences. Moreover, the specification, on pages 24-31, has discussed that each of the sequences is differentially expressed from a predicted gene, in *C. elegans*, in response to cadmium exposure. This suggests that the sequences set forth in SEQ ID NOs: 34, 50, 40 and 14 are alternatively spliced from predicted gene

F35E8.11 and encode different proteins each having a different chemical structure and a different function. In light of the above reasoning, it is maintained that Inventions I-IV are distinct and the sequences embraced by each are separately searched. Absent evidence to the contrary, showing that SEQ ID NOs 34, 50, 40 and 14 do not encode different proteins, the restriction requirement over Groups I-IV is maintained for the reasons of record. See page 2 of the Office action mailed on 10/22/02.

In response, to Applicant's arguments that up to 10 independent and distinct sequences may be examined in a single application, the Examiner asserts that distinct sequences may be properly restricted each from the other. See below. MPEP 803.04 states: Nucleotide sequences encoding different proteins are structurally distinct chemical compounds and are unrelated to one another. These sequences are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U.S.C. 121. Absent evidence to the contrary, each such nucleotide sequence is presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.141 et seq. Nevertheless, to further aid the biotechnology industry in protecting its intellectual property without creating an undue burden on the Office, the Commissioner has decided sua sponte to partially waive the requirements of 37 CFR 1.141 et seq. and permit a reasonable number of such nucleotide sequences to be claimed in a single application. See Examination of Patent Applications Containing Nucleotide Sequences, 1192 O.G. 68 (November 19, 1996).

Although the MPEP deems that up to ten nucleotide sequences may be searched without restriction, it has recently been decided by the Director of Biotechnology at the USPTO that searching more than one sequence per application will place an undue burden upon the Examiner and the Office. For this reason, restriction to ONE SEQUENCE is being applied to all applications at this time.

Please note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

Drawings

New corrected drawings are required in this application because of the objections by the Draftsman as set forth in the PTO-948 attached to Paper No. 8, mailed on 1/19/01. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See page 9 of the specification.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119 (e) as follows: An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number. It appears that Applicants are claiming priority to provisional application 60/109,281, however the first sentence of the specification does not refer to the provisional application.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 7, 11 and 15 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. The previous rejection is maintained for the reasons of record advanced on pages 3-5 of the Office action mailed on 10/22/02..

Applicant's arguments filed 3/4/03 have been fully considered but they are not persuasive. Applicants have argued that SEQ ID NO: 40 (DDRT16) is derived from a cadmium-responsive gene; the utility of SEQ ID NO: 40 being that it can serve as a biomonitor for cadmium exposure. See page 3 of the amendment. Applicants have provided the Liao reference (2002) in support of their assertions of the utility of SEQ ID NO: 40 and specifically point to page 42050, left column of Liao to establish the relationship of SEQ ID NO: 40 (DDRT16) to cdr-1, a cadmium-responsive gene. Applicants have also provided the Cioci reference in support of their assertions as to the utility of transgenic *C. elegans* strains as biomonitors.

In response, the Examiner maintains that the invention as claimed lacks a specific and substantial or well-established utility. It is maintained that the evidence of record at the time the claimed invention was filed taught what the polynucleotide of SEQ ID NO: 40 does, established a relationship between SEQ ID NO: 40 and any disease, or identified a protein (and its function) encoded by the nucleotide sequence of SEQ ID NO: 40. See the Office action mailed on 10/22/02 on pages 3-5. The evidence of record at the time the claimed invention was filed provided general assertions (probe for diagnosing a disease, primers for PCR, treatment of disease) as to the utility of the nucleotide sequence set forth in SEQ ID NO: 40 that could be applied to other

polynucleotide sequences. The asserted utility of SEQ ID NO: 40 to function as a biomonitor, as argued by Applicants, appears to be unsupported. On page 12 of the specification biomonitors are discussed in general. The discussion of biomonitors is limited to kits comprising primers or oligonucleotides that can be used to amplify and/or detect cadmium-responsive mRNAs. However, the discussion of biomonitors does not provide a utility for a cadmium-responsive mRNA or cDNA as claimed. As such the asserted utilities provided by the evidence of record are not specific for the nucleotide sequence set forth in SEQ ID NO: 40. See page 4 of the Office action mailed on 10/22/02.

The Liao reference provided by Applicants in support of the asserted utility of the claimed invention teaches that the nucleotide sequence set forth in SEQ ID NO: 40 (DDRT16) is actually a partial cDNA sequence (EST) of a newly discovered *C.elegans* gene, CDR-1. See page 42050, column 1 in the experimental procedures, in the section entitled isolation of the CDR-1 cDNA. Liao goes on to discuss that the full length CDR-1 cDNA was derived from the EST DDRT16 using 5' RACE. See page 42052, in column 2, at the beginning of the results section. Liao generally teaches expression of a "variety of proteins" is upregulated in response to cadmium and that the functions of these proteins can be broadly defined. See page 42049, in column 2, in the first full paragraph. It appears that Liao is suggesting that cadmium responsiveness is a general phenomenon, which is applicable to many genes [also see the specification on pages 3-4 which discusses the different functions of proteins encoded by cadmium-responsive genes]. It is noted that the publication date of the Liao reference is 11/1/02

and that the effective filing date of the instant application is 11/20/98. It is clear from the evidence of record that at the time the claimed invention was filed that the full-length sequence of the CDR-1 gene was not available. Moreover, the Liao reference has not provided utility for a partial cDNA sequence of the CDR-1 gene, such as DDRT16 (SEQ ID NO: 40). It would appear that the nucleotide sequence set forth in SEQ ID NO: 40 does not encode a functional protein as it is only a partial cDNA sequence. Furthermore, evidence of record is lacking, which suggests that SEQ ID NO: 40, independent of the other coding sequences of the CDR-1 gene, can be expressed in cells. Thus, it appears that the nucleotide sequence set forth in SEQ ID NO: 40 can only be used for further research (such as for obtaining a full length cDNA sequence), which does not meet the requirement for utility under 35 U.S.C. 101. In Brenner, the Court held that materials to be used as an object of research or methods of using those materials as an object for research have raised issues as to whether those materials possess a real world context of use of substantial utility. See Brenner v. Manson, 148 USPQ 689 (US SupCt 1966).

The Cioci reference generally discusses the use of transgenic *C. elegans* as biomonitors (also see page 13 of the specification) for transition metal contamination, such as cadmium, mercury, zinc, and nickel. Cioci exemplifies a transgenic *C. elegans* whose genome comprises a reporter construct containing a promoter of the metallothionein-2 (mtl-2) gene operably linked to the coding sequence of the reporter gene β-galactosidase. Cioci suggests that exposure to metals results in transcription of metallothioneins within 30 minutes. In the context of a transgenic *C. elegans* upon

exposure to metals activates the metallothionein promoter to upregulate transcription of β-galactosidase. However, Cioci does not discuss DDRT16 (SEQ ID NO: 40). As such Cioci has not provided support for the asserted utilities of SEQ ID NO: 40. In any event, the teachings of Cioci suggest that a promoter sequence of a metal responsive gene is important for detecting metal exposure as it is the promoter sequence that is activated upon exposure to metals, resulting in upregulation of transcription of a coding sequence. The nucleotide sequence set forth in SEQ ID NO: 40 is a partial coding sequence and does not appear able to express itself in response to cadmium exposure. In light of such, it would appear that use of the nucleotide sequence of SEQ ID NO: 40 as a transgene in a transgenic *C. elegans* to detect cadmium exposure does not meet the utility requirement under 35 U.S.C. 101.

As such, the evidence of record has not provided a specific and substantial or well-established utility for the nucleotide sequence set forth in SEQ ID NO: 40. Accordingly, the previous rejection is maintained for the reasons of record and as discussed in the preceding paragraphs.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7, 11 and 15 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and

substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. The previous rejection is maintained for the reasons of record and as discussed above in the preceding utility rejection.

Applicant's arguments filed 3/4/03 have been fully considered but they are not persuasive. Applicants have argued that one utility of the claimed invention is in the context of a biomonitor, wherein on exposure to cadmium, mRNA levels are significantly increased. Applicants have further argued that the instant inventions embraces use of transgenic organisms comprising cadmium-responsive sequences as biomonitors to measure the levels of cadmium. See page 4 of the amendment.

In response, the Examiner asserts that the evidence of record has not taught how to use the nucleotide sequence set forth in SEQ ID NO: 40 (DDRT16) for the reasons of record set forth in the utility rejection as set forth on pages 3-5 of the Office action mailed on 10/22/02 and as discussed above. Accordingly, the rejection is maintained.

Claim 15 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The previous rejection is maintained for the reasons of record advanced on pages 6-7 of the Office action mailed on 10/22/02.

Applicant's arguments filed 3/4/03 have been fully considered but they are not persuasive. Applicants have argued that they were in possession of a C. elegans whose genome comprises the nucleotide sequence set forth in SEQ ID NO: 40. Applicants have pointed to original claim 4, pages 13-14, and Table II of the specification for support of their arguments.

In response, the Examiner maintains that the specification provides no implicit or explicit support for a *C. elegans* the genome of which has been engineered to include the nucleotide sequence of SEQ ID NO: 40 (DDRT16). Applicants are reminded that it is their burden to show where the specification supports any amendments to the claims. See 37 CFR 1.121 (b)(2)(iii), the MPEP 714.02, 3rd paragraph, last sentence and also the MPEP 2163.07, last sentence.

Original claim 4 does not provide support for the claimed *C. elegans*. Claim 4, is directed to a *C. elegans* whose genome comprises a cadmium-responsive gene while the instantly claimed C. elegans has a genome that comprises the nucleotide sequence set forth in SEQ ID NO: 40. A cadmium-responsive gene is a broad recitation encompassing the entire genus of cadmium-responsive genes but does not necessarily support individual species within the genus. Moreover, a partial cDNA sequence, such as SEQ ID NO: 40 (DDRT16) is not a gene. Therefore, the recitation of cadmium-responsive gene does not support the nucleotide sequence set forth in SEQ ID NO: 40 (DDRT16).

The specification on pages 13-14 discusses transgenic organisms, particularly *C. elegans*, the genome of which has been engineered to include a cadmium-responsive

gene. However, the discussion on pages 13-14 does not mention SEQ ID NO: 40 (DDRT16) and is limited to general recitations of cadmium-responsive genes. Thus, the discussion on pages 13-14 of the specification relating to transgenic organisms does not support a transgenic *C. elegans* whose genome comprises the nucleotide sequence set forth in SEQ ID NO: 40.

Finally, Table II on pages 26-27 does not relate to transgenic *C. elegans*. Table II shows the various species of differentially expressed mRNAs isolated from wild-type *C. elegans* exposed to cadmium.

Accordingly, the previous rejection is maintained for the reasons of record and as discussed in the preceding paragraphs.

Conclusion

No claim is allowed. The claims appear to be free of the prior art of record but are subject to other rejections.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at 703-305-4051. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703) 308-4242 and (703) 305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to Dianiece Jacobs whose telephone number is (703) 305-3388.

Peter Paras, Jr.
Art Unit 1632

PETER PARAS
PATENT EXAMINER